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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,387	10/25/2005	Yoseph Shaaltiel	30570	1887

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
02/18/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,387	SHAALTIEL ET AL.	
	Examiner	Art Unit	
	DELIA M. RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *98,100,106,107,109,114,115,117,120,124,125,127,128 and 142-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *98,100,106,107,109,114,115,117,120,124,125,127,128 and 142-146* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *alignments*.

DETAILED ACTION

Status of the Application

Claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146 are pending.

The indicated allowability of claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146 is withdrawn in view of the newly discovered reference(s) of Frijters et al. (NL-1012782, published 2/6/2001). Rejections based on the newly cited reference(s) follow.

The Examiner's amendment of 10/16/2009 canceling claims 150-153 and amending claims 98, 115, 142-143, and 146 has been entered. The pending claims are as follows:

98. An isolated human lysosomal protein comprising at least one xylose residue and at least one exposed mannose residue, wherein said human lysosomal protein comprises an amino acid sequence encoded by the nucleic acid as set forth in SEQ ID NO: 7, and wherein said human lysosomal protein is contiguously linked at its C-terminus to a vacuolar targeting signal peptide and at its N-terminus to an N-terminal endoplasmic reticulum signal peptide, wherein said endoplasmic reticulum signal peptide comprises SEQ ID NO: 1.

99. (Canceled)

100. (Previously Presented) The human lysosomal protein of claim 98, further comprising at least one fucose residue having an alpha (1-3) glycosidic bond.

101-105. (Canceled)

106. (Previously Presented) The human lysosomal protein of claim 98, wherein said vacuolar targeting signal peptide is a basic tobacco chitinase A gene vacuolar targeting signal.

107. (Previously Presented) The human lysosomal protein of claim 106, wherein said vacuolar targeting signal peptide comprises SEQ ID NO: 2.

108. (canceled)

109. (Previously Presented) The human lysosomal protein of claim 98, wherein said amino acid sequence comprises the amino acid sequence as set forth in SEQ ID NO: 8.

110-113. (Canceled)

114. (Previously Presented) A pharmaceutical composition comprising the human lysosomal protein of claim 98 and a pharmaceutically acceptable carrier.

115. A plant cell preparation comprising a human lysosomal protein comprising at least one xylose residue and at least one exposed mannose residue, wherein said human lysosomal protein comprises an amino acid sequence encoded by the nucleic acid as set forth in SEQ ID NO: 7, and wherein said human lysosomal protein is contiguously linked at its C-terminus to a vacuolar targeting signal peptide and at its N-terminus to an N-terminal endoplasmic reticulum signal peptide, wherein said endoplasmic reticulum signal peptide comprises SEQ ID NO: 1.

116. (Canceled)

117. (Previously Presented) The plant cell preparation of claim 115, further comprising at least one fucose residue having an alpha (1-3) glycosidic bond.

118-119. (Canceled)

120. (Previously Presented) The plant cell preparation of claim 115, wherein said human lysosomal protein comprises the amino acid sequence as set forth in SEQ ID NO: 8.

121-123. (Canceled)

124. (Previously Presented) The plant cell preparation of claim 115, wherein said vacuolar targeting signal peptide is a basic tobacco chitinase A gene vacuolar targeting signal.

125. (Previously Presented) The plant cell preparation of claim 124, wherein said vacuolar targeting signal peptide comprises SEQ ID NO: 2.

126. (Canceled)

127. (Previously Amended) The plant cell preparation of claim 115, wherein the main glycan structure of the lysosomal protein of said plant cell preparation comprises at least one xylose residue and at least one exposed mannose residue, as measured by linkage analysis.

128. (Previously Presented) A pharmaceutical composition comprising the plant cell preparation of claim 115 and a pharmaceutically acceptable carrier.

129-141. (Canceled)

142. An isolated human lysosomal protein comprising a human glucocerebrosidase which comprises the amino acid sequence as set forth in SEQ ID NO: 8, wherein said human glucocerebrosidase is linked at its C-terminus to the vacuolar signal peptide as set forth in SEQ ID NO: 2 and at its N-terminus to the endoplasmic reticulum signal peptide as set forth in SEQ ID NO: 1.

143. An isolated human lysosomal protein comprising a human glucocerebrosidase which comprises the amino acid sequence as set forth in SEQ ID NO: 14.

144. (Previously Presented) A pharmaceutical composition comprising the human lysosomal protein of claim 142 and a pharmaceutically acceptable carrier.

145. (Previously Presented) A pharmaceutical composition comprising the human lysosomal protein of claim 143 and a pharmaceutically acceptable carrier.

146. An isolated human lysosomal protein comprising a human glucocerebrosidase which comprises the amino acid sequence as set forth in SEQ ID NO: 8, wherein said human glucocerebrosidase comprises at least one exposed mannose residue, and is linked at its C-terminus to a vacuolar targeting signal peptide and at its N-terminus to the endoplasmic reticulum signal peptide as set forth in SEQ ID NO: 1.

147-153. (Canceled)

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 11/15/2009 is acknowledged. However, the submission is not in compliance with the provisions of 37 CFR 1.97 for the reasons indicated in the Office communication mailed on 11/25/2009. Accordingly, the information disclosure statement has not been considered by the examiner.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garger et al. (U.S. Publication 2002/0088024, published 7/4/2001; application No. 09/993059 filed on 11/13/2001), as evidenced by GenBank accession number P04062 GLCM_HUMAN GI:121283 (April 1, 1993) in view of Boller et al. (U.S. Patent No. 6054637, issued 4/25/2000) and further in view of Frijters et al. (NL-1012782, published 2/6/2001).

Garger et al. teach the recombinant production of human glucocerebrosidase in transgenic tobacco plants (Examples 1-7; called rGCB). Garger et al. teach (page 4, paragraph [0032]) that their human glucocerebrosidase is that disclosed by Tsuji et al. (J. Biol. Chem. 261:50-53, 1986) and Sorge et al. (PNAS 82:7289-7293, 1985). Thus, the human glucocerebrosidase of Garger et al. comprises SEQ ID NO: 8 as evidenced by GenBank accession number P04062, locus GLCM_HUMAN, GI:121283, since this GenBank entry cites Tsuji et al. and Sorge et al. as references associated with the protein disclosed in that entry. See attached alignment. Garger et al. also teach the enzymatic removal of sialic acid, galactose, and N-acetylglucosamine residues to prepare glucocerebrosidase for therapy (page 14, paragraph [0164], lines 12-15; page 1, paragraph [0006], lines 18-26) and that their rGCB co migrates with the mannose-terminal therapeutic glycoform. Garger et al. teach that one of the uses for the recombinant rGCB produced in plants is for therapy (page 6, paragraph [0045]). As known in the art, xylose residues and core alpha (1-3) fucose residues are added to proteins in plants during the glycosylation process. Garger et al. teach that the rGCB produced in transgenic tobacco plants has xylose and fucose residues (page 13, paragraph [0125], last two sentences). Also, as known in the art, removal of sialic acid, galactose, and N-acetylglucosamine residues would result in mannose residues being exposed. The instant reference further teaches the purification of the rGCB (Example 5). Garger et al. do not teach the human glucocerebrosidase linked at the N-terminus to an endoplasmic reticulum signal peptide and linked at the C-terminus to the basic tobacco chitinase A gene vacuolar targeting signal peptide.

Boller et al. teach that one of the advantages in directing proteins to the vacuole is due to the fact that vacuoles constitute the largest storage compartment in plants for dissolved substances (column 2, line 57-column 3, line 1). Boller et al. teach several signal peptides for vacuolar sorting including a tobacco chitinase gene vacuolar targeting signal peptide which comprises SEQ ID NO: 2 (SEQ ID NO: 29 in that patent). See attached alignment. Boller et al. disclose adding the DNA encoding the vacuolar targeting

signal peptide at the 3' end of any desirable expressible DNA. As such, Boller et al. teach adding the vacuolar signal peptide to the C-terminus of any desired protein (column 8, lines 38-52). Boller et al. do not teach the polypeptide of SEQ ID NO: 8.

Frijters et al. teach an N-terminal endoplasmic reticulum signal sequence which is identical to that of SEQ ID NO: 1 (page 17, lines 10-18; MKTNLFLFLIFSLLLSLSSAEF; SEQ ID NO: 3, page 30) which was linked to an *A. victoria* GFP variant to direct this variant to the ER. See attached alignment. Frijters et al. do not teach the protein of SEQ ID NO: 8.

Claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146 are directed to (1) a protein which comprises SEQ ID NO: 14, (2) a protein which is encoded by the polynucleotide of SEQ ID NO: 7, wherein said protein comprises SEQ ID NO: 8, and wherein said protein is contiguously linked at the N-terminus to the endoplasmic reticulum signal peptide of SEQ ID NO: 1 and contiguously linked at the C-terminus to the vacuolar targeting signal peptide of SEQ ID NO: 2, (3) a plant cell preparation comprising (1) or (2), wherein the protein of (1) or (2) contains a xylose residue, exposed mannose residues and a fucose residue having an alpha (1-3) glycosidic bond, and (4) a pharmaceutical composition comprising the polypeptides of (1) or (2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a fusion protein comprising the endoplasmic reticulum signal peptide of Frijters et al. linked to the N-terminus of the human glucocerebrosidase of Garger et al. and the vacuolar signal peptide of Boller et al. at the C-terminus of the human glucocerebrosidase of Garger et al. A person of ordinary skill in the art is motivated to construct such fusion protein because (1) Boller et al. teach the advantages of directing a desired protein to the vacuole of a plant, and (2) the human glucocerebrosidase of Garger et al. requires glycosylation. As known in the art and taught by Garger et al., the initial steps in the glycosylation process take place in the endoplasmic reticulum (page 3, paragraph [0025]). Therefore, adding an ER signal to the human glucocerebrosidase of Garger et al. would direct this protein to the ER for

glycosylation. One of ordinary skill in the art has a reasonable expectation of success at making the fusion protein of Garger et al., Boller et al. and Frijters et al. since Boller et al. and Frijters et al. teach fusion proteins comprising said signal peptides, and the use of fusion proteins comprising the desired protein linked to heterologous signal peptides is well known and widely practiced in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 39, 45 of copending Application No. 11/790991. This rejection was previously withdrawn in the Office action mailed on 10/16/2009 since this was the only rejection remaining at that time. In view of the fact that the allowability of the instant claims has been withdrawn, this rejection is hereby reintroduced.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146

are directed to (1) a protein which comprises SEQ ID NO: 14, (2) a protein which is encoded by the polynucleotide of SEQ ID NO: 7, wherein said protein comprises SEQ ID NO: 8, and wherein said protein is contiguously linked at the N-terminus to the endoplasmic reticulum signal peptide of SEQ ID NO: 1 and contiguously linked at the C-terminus to the vacuolar targeting signal peptide of SEQ ID NO: 2, (3) a plant cell preparation comprising (1) or (2), wherein the protein of (1) or (2) contains a xylose residue, exposed mannose residues and a fucose residue having an alpha (1-3) glycosidic bond, and (4) a pharmaceutical composition comprising the polypeptides of (1) or (2). Claims 39 and 45 of copending application No. 11/790991 are directed to a human lysosomal protein comprising SEQ ID NO: 8 comprising one xylose residue and one exposed mannose residue, and a pharmaceutical composition comprising said human lysosomal protein. The specification of copending application No. 11/790991 teaches as a preferred embodiment of the invention, the polypeptide of SEQ ID NO: 14, which is the protein of SEQ ID NO: 8 further comprising the signal peptide of SEQ ID NO: 1 at the N-terminus of SEQ ID NO: 8 and the vacuolar targeting signal peptide of SEQ ID NO: 2 at the C-terminus of SEQ ID NO: 8. The specification also discloses as a preferred embodiment of the invention, the plant-glycosylated protein of SEQ ID NO: 14, wherein said protein comprises exposed mannose residues, a xylose residue and a fucose residue. Therefore, in view of the preferred embodiments disclosed in the specification of copending Application No. 11/790991, the invention of claims 98, 100, 106-107, 109, 114-115, 117, 120, 124-125, 127-128, 142-146 are deemed an obvious variation of the invention of claims 39, 45 of copending Application No. 11/790991.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

7. No claim is in condition for allowance.

8. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

9. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (571) 272-0811. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner
Art Unit 1652

DR
February 18, 2010